**Peer Review File**

**Article information:** https://dx.doi.org/10.21037/jtd-23-480

**Reviewer A**

The manuscript “Global, regional, and national time trends in disability-adjusted life years, mortality, and variable risk factors of non-rheumatic calcified aortic valve disease, 1990–2019: an age-period-cohort analysis of the Global Burden of Disease 2019 study” is showing CAVD has resulted in a high burden of disease for people worldwide. It is important to describe these results to the scientific community, even though the manuscript is not easy to read and some points are not clear due to the language used. A proofreading of English is necessary through the article. However, there are several major comments needs to improved.

Major:

1. Figure 3 showed the relationship between SDI levels and the 2019 ASR for CAVD in 204 countries and territories. However, this figure only showed the relationship between the changes in mortality and the SDI, such as the incidence and the DALYS of CAVD had not been displayed, which was also concerned by ours. In addition, the correlation between the global distribution of ASR and SDI Levels should also be displayed.

Reply 1: Thank you for your thoughtful suggestion. Your suggestions are very important to improve the quality of our papers. The relationship between DALYS levels and SDI in CAVD has been added to the Supplementary materials as "Figure S2 Relationship between SDI levels and the 2019 Age-standardized DALYs rate for CAVD in 204 countries and territories (A) and the percentage change in rate between 1990 and 2019 (B)". Although the prevalence of CAVD is important, the focus of this study was on an already diseased population, so this aspect may not be addressed. In addition, due to the limitation of the length of the paper, it may not be possible to include an exploration of this aspect in this study. For the correlation study between the global distribution of ASR and SDI levels, it is difficult to analyze the correlation study because each country has different national conditions, and the treatment of diseases is influenced by aspects including the natural environment, cultural traditions, and the level of economic development, which vary significantly from country to country. It can also be seen from Figure 3 that the ASR and SDI levels are not fully correlated across countries. However, we show the relationship between ASR and SDI levels in Figure 3 for 204 countries worldwide, which we hope can help countries to develop individualized disease response policies.

2. Similarly, Figure 4 only showed the relationship between mortality and the different degree of SDI, and obtained the conclusions of the mortality of the high SDI region in the elderly, but this may be more related to the local medical level. The incidence and DALYs of CAVD and

the correlation between SDI had not visualized.

Reply 2: Thank you very much for asking this question. The relationship between DALYs and SDI in CAVD has been added to the Supplementary Material. It can be found in "Figure S3 Trends in the age distribution of DALYs lost owing to CAVD across countries and regions with different SDI for the entire population and male and female populations, 1990-2019." However, because the prevalence is beyond the scope of this article and because of the limitations of the paper's length, it may not be possible to discuss this issue in depth.

3. Meantime, the original data of GBD was not available in all countries, particularly in low SDI regions, could affect the precision of estimates, especially in this manuscript that discuss the SDI area and disease.

Reply 3: Thank you for your thoughtful suggestion. As you mentioned, the GBD data has limitations due to the limited availability of raw data for low- and middle-income countries, while the estimates are from high-resource settings. We have added this description to the "Limitations" section of the discussion. However, a Pubmed search for "GBD" yielded 2,334 documents, proving this database is reliable. However, it should also be emphasized that further validation for national contexts is needed before our ideas can be translated into public health policy.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 14, lines 471 to 481).

4. More importantly, after searching on PUBMED, we found that there are two articles based on the 2019 GBD database analysis of NRVHDS. Therefore, this article is not innovative enough.

Reply 4: Thank you very much for asking this relevant question. As you said, there have indeed been articles analyzing NRVHDS based on the 2019 GBD database. However, we believe this may not affect the value of our study. First, the disease characteristics and patient survival of the major subtypes of NRVHDS, CAVD, and degenerative mitral valve disease (DMVD) vary widely and require further analyses specific to CAVD. Second, these analyses do not distinguish the relative contribution of age, period, and cohort to the impact of mortality. There is also a lack of reliable evidence on trends in the primary variable risk factors for CAVD across countries and regions, which is essential to suggest effective prevention and treatment strategies. Therefore, our study remains significant in exploring the global disease burden of CAVD and the development of individualized countermeasures in each country.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 3, lines 97 to 118).

Minor:

1. The description of Figure 2 needs to be specific, e.g., Figure 2A seems to display age standardized mortality rate of CAVD in 2019. Therefore, the abbreviation should not be ASR but ASMR.

Reply: Thank you for your thoughtful suggestion. We have made changes to the manuscript.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 21, lines 644 to 647).

**Reviewer B**

First, the abstract needs some revisions. The background did not describe the potential public health significance of this analysis and did not briefly comment the limitations of prior studies. The methods need to describe the data source, variables in the database, and how the APC analysis was performed. The results need to first report the incidence rates, mortality rates due to non-rheumatic calcified aortic valve disease, and findings on the age, period, and birth cohort effects should be reported. The conclusion should not repeat the findings again and please have detailed comments for the public health implications of the findings.

Reply: Thank you very much for your valuable and insightful comment. Your suggestion is very important to improve the quality of our paper. We have already rewritten the abstract section based on the suggestions.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 2, lines 35 to 74).

Second, in the introduction of the main text, I do not find a detailed review on what has been known on the disease burden, mortality, and risk factors of CAVD. The authors have no comments on the limitations and knowledge gaps of prior studies. The authors also did not explain the importance of data on the age, period, and cohort effects on CAVD and what the potential public health significance is. As a basis for this study, the authors need some introduction on the theory of APC model and what the limitations of APC analysis.

Reply 2: Thank you very much for asking this relevant question. Your recommendations are very important. As you said, a detailed review of the burden of disease, mortality, and risk factors for CAVD is critical, as well as a review of previous studies' limitations and knowledge gaps. And the theory of the APC model, the limitations of the analysis, and the importance of data on age, period, and cohort effects also need to be described. We have changed the introduction and methods sections extensively in response to suggestions.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 3, lines 80 to 118; page 5, lines 165 to 208).

Third, in the methodology of the main text, it is very important to describe the GBD data in detail including the representativeness and how the data were generated. Because these data are based on mathematical model with broad uncertain confidence intervals, the authors need to explain whether the data can be directly used to do APC analysis. For the countries of low SDI, many countries have no vital registration systems or high-quality systems, there is quality concern regarding their data. The APC analysis based on their data is not convincing.

Reply 3: Thank you very much for your valuable and insightful comment. We have added a detailed description of the GBD database in the text. The data pre-processing process for GBD

data before it is used in the APC model for analysis is also described. To show how we use the APC model to analyze GBD data. GBD raw data may not be available for some low SDI countries. This is an inherent drawback of GBD data, which we discuss in the limitations. However, a search of the PubMed database provides access to more than 2000 studies based on the GBD database, which can demonstrate the reliability of these data. Of course, in-depth exploration in the national context is needed before our views can be translated into public health policy. This is very important.

Changes in the text: We have added content regarding these points in the revised manuscript (Manuscript file, page 4, lines 130 to 141; page 6, lines 181 to 191; page 14, lines 471 to 481).